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Original Article

Lung deposition of inhaled tobramycin with eFlow rapid/LC Plus jet nebuliser in healthy and cystic fibrosis subjects

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Abstract

Background: Reducing nebulisation times for tobramycin solution for inhalation in cystic fibrosis (CF) may improve compliance.
Methods: In this single-dose, open-label, two-way crossover study, 13 subjects (7 CF, 6 healthy) were randomised to receive tobramycin via eFlow *rapid* or LC Plus jet nebuliser. Drug deposition in the lung using gamma scintigraphic imaging, nebulisation times, pharmacokinetics, and safety were evaluated.
Results: In CF patients, whole-lung deposition was 40% less with the eFlow *rapid* compared with LC Plus nebulisers was (8.9±0.8%, and 15.1±6.0%, $p>0.05$). Nebulisation time was shorter with eFlow *rapid* compared to LC Plus (7.0 min versus 20.0 min, $p<0.05$). Lung deposition in healthy subjects was comparable between both devices.
Conclusions: eFlow *rapid* reduces the nebulisation time of tobramycin and can potentially improved compliance in patients with CF.

Keywords: Cystic fibrosis; Nebuliser; Tobramycin; Aerosol; Pharmacokinetics; Pharmacoscintigraphy

1. Introduction

Patients with cystic fibrosis (CF) often become chronically infected with *Pseudomonas aeruginosa*. This chronic infection is associated with acute exacerbations and progressive lung damage necessitating treatment with parenteral antibiotics [1]. The standard therapy for *P. aeruginosa* respiratory infections is parenteral antipseudomonal antibiotics, which penetrate poorly into the endobronchial space [2]. Therefore, inhalation of aerosolised antibiotics enables delivery of high concentrations directly to the lungs with minimal systemic absorption and toxicity [3,4]. The most commonly used aerosolised antibiotics are tobramycin and colistimethate sodium, which can be delivered twice daily for prolonged periods of time [3]. A preservative-free and stable formulation of tobramycin solution (TOBI®, 300 mg in 5 mL of 1/4 normal saline) is available for the long-term management of *P. aeruginosa* infection in patients with CF [5,6]. It has been studied extensively [7] and is recommended to be administered using the LC Plus jet nebuliser (PARI GmbH, Stranberg, Germany) powered by a suitable compressor, which delivers a flow rate of 4–6 L/min and/or a back pressure of 110–217 kPa.

Administration with this nebuliser takes approximately 15–20 min [8]. Patient compliance and acceptance of a twice-daily tobramycin regimen may be improved by decreasing the nebulisation time using an alternative drug delivery system [9]. A wide range of commercially available nebulisers have been tested as alternatives to administration of tobramycin [10,11]. The battery-driven eFlow *rapid* nebuliser (PARI Respiratory Equipment Inc., Midlothian, VA, USA) is designed to deliver liquid or suspension formulations for inhalation more rapidly than the jet nebulisers [8,12].

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The primary objective of this exploratory study was to assess the *in vivo* lung deposition of 300 mg tobramycin inhaled using the PARI eFlow *rapid* electronic nebuliser (with no compressor) in comparison with the deposition of 300 mg tobramycin inhaled using the PARI LC Plus jet nebuliser (with an appropriate compressor). Nebulisation times, safety, drug deposition, and pharmacokinetic (PK) parameters of tobramycin were also assessed.

2. Methods

2.1. Study design

This was a phase I, multi-centre, randomised, single-dose, open-label, crossover study of tobramycin (TOBI®, 300 mg in 5 mL of 1/4 normal saline) in healthy volunteers and CF patients. The protocol was approved by the ethics committee of each study centre (University Hospital of North Staffordshire, Northern General Hospital, Sheffield and Pharmaceutical Profiles Ltd., Nottingham). Written informed consent was obtained from all subjects.

2.2. Study population

2.2.1. Inclusion criteria

Healthy male and female volunteers aged between 18 and 65 years, within ±25% of their ideal weight (using the Body Mass Index [BMI] method) and with an initial percent predicted forced expiratory volume at 1 s (%FEV_1) ≥ 80% were included. In addition, male and female CF patients aged 18–65 years with chronic *P. aeruginosa* infection and a screening % predicted $FEV_1 \geq 25\%$ were invited to take part. The use of any investigational treatment or new medication within 1 month prior to screening and throughout the study was prohibited. Previous use of tobramycin and other regular medicines was documented. A 1-week washout period for all subjects receiving tobramycin or other aminoglycoside antibiotics or a 2-day washout period for those receiving colistimethate sodium was required prior to enrolment.

2.2.2. Exclusion criteria

Subjects were excluded if they had a history of smoking or alcoholism, had a known hypersensitivity to aminoglycosides or salbutamol, or had received administration of a loop diuretic within 7 days prior to screening. Subjects with impaired renal function or other clinically significant abnormal biochemistry, haematology, or urinalysis values were also excluded.

2.3. Study duration and treatment assignment

The study duration was approximately 6 weeks: a 4-week screening period and two treatment periods with follow-up within 14 days of the last dose. A single dose of aerosolised tobramycin radiolabelled with sterile technetium bound to diethylene triamine penta acetic acid (99mTc DTPA) was delivered via either the eFlow *rapid* nebuliser (experimental treatment A) or the LC Plus nebuliser (control treatment B). Stop times of nebulisation are defined as the time when the nebuliser becomes dry and automatically stops (eFlow *rapid* nebuliser) or when the nebuliser begins to sputter and nebulisation is stopped manually (LC Plus nebuliser). All subjects were randomly assigned (1:1) to receive treatments in the order AB or BA. The doses were administered on the morning of Day 1 of each of the two treatment periods, which were separated by a minimum washout period of 72 h. All subjects were pre-treated with 200 μg of inhaled salbutamol 15–60 min before tobramycin administration, but after the pre-dose spirometry test. If bronchoconstriction occurred after inhalation of tobramycin, the salbutamol was administered as required.

2.4. Aerosol delivery assessments

Deposition patterns of inhaled radiolabelled tobramycin were determined using two-dimensional gamma scintigraphic imaging methodology [13]. Lung, oropharyngeal, and abdominal radioactivity were measured from images obtained immediately after the completion of each tobramycin dose using a gamma camera (General Electric Maxicamera, GE Medical Systems, Milwaukee, WI, USA). Each subject underwent transmission scans of the head and thorax using a flood field source containing 57-Cobalt (^{57}Co) to correct for attenuation of gamma rays by overlying tissues. The lung scan outlines were used to divide the lung images of each subject into six concentric lung-shaped regions radiating from the hilum (Fig. 1; zones 1–6) to determine the amount of aerosolised tobramycin deposited in each zone [14,15]. All images were recorded using Micas X-Plus software (Bartec Technologies, Camberley, Surrey, UK) installed on a UNIX-based computer system and were stored for subsequent analysis and archiving.

The scintigraphic data obtained were corrected for background radioactivity, radioactive decay, and tissue attenuation [15]. The manipulation and calculation of radioactivity counts were achieved with the validated custom-written software. The primary aerosol delivery parameter of interest was the whole-

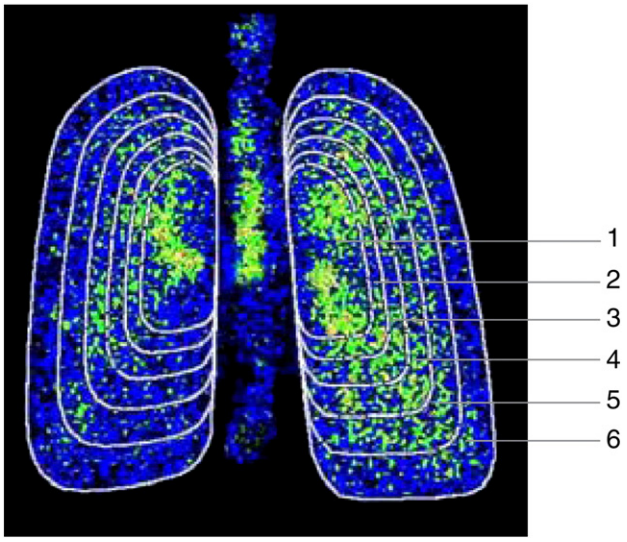

Fig. 1. Activity distribution of radiolabelled tobramycin in lung regions. Six lung-shaped regions: regions 1–4 = mainly large conducting airways; regions 5 and 6 = mainly small airways and alveoli. Adapted from Newman et al. [13].

lung deposition (expressed as% of dose and amount of dose in mg). The deposition counts in each area were expressed as a percentage of the metered dose determined from the sum of the total body radioactivity counts plus the inhaler and exhalation filter deposition counts. To facilitate interpretation of the data, the amounts of drug deposited in milligrams for each of the deposition parameters were estimated.

Whole-lung deposition was evaluated descriptively for differences between the aerosol delivery systems and between the subject groups. Additional aerosol delivery measures of interest were deposition in lung zones 1–6, oropharynx (including oesophagus and stomach), nebulisers, and exhalation filters (level of radio aerosol in exhaled air) [14].

Nebulisation times and dose interruptions were also recorded.

2.5. Pharmacokinetic assessments

Venous blood samples were collected pre-dose and at 0.5, 1, 2, 4 and 8 h post-inhalation of tobramycin. Serum was harvested and frozen at less than −70 °C until analysis. Concentrations of tobramycin in serum were analysed with a modified fluorescence polarisation immunoassay [16] using the Abbott TDx/TDxFLx system (Abbott Laboratories, Abbott Park, IL, USA). PK parameters included area under the curve from time 0 to 8 h (AUC_{0-8}, [μg h/mL]), peak concentration (C_{max}, μg/mL), time to reach maximum concentration (t_{max}), and half-life ($t_{1/2}$). The occurrence of high serum tobramycin concentrations that may be associated with toxicity was assessed. The thresholds were pre-defined in the protocol as trough concentrations >2 μg/mL, C_{max} >12 μg/mL, and concentrations at any other time post-dose >4 μg/mL [17].

2.6. Safety assessments

2.6.1. Analysis of bronchospasm

Changes in pulmonary function were used to assess airway reactivity after the drug inhalations. Reductions in $\%FEV_1$ by < 20% were deemed clinically insignificant, those ≥20% but <30% were considered to be clinically significant and those ≥30% were considered to indicate severe bronchospasm.

2.6.2. Adverse events

All adverse events (AEs) were recorded, including the potential for increased risk of systemic toxicity as determined by serum concentrations of tobramycin.

2.7. Statistical analyses

All subjects who received at least one dose of medication were included in the intention-to-treat population and were evaluable for safety and aerosol delivery characteristics. Only those who participated in both arms of the trial and provided appropriate samples and measurements were included in the deposition-evaluable and pharmacokinetics-evaluable populations. The aim of this exploratory study was to look for trends in nebulisation time and PK parameters produced by the two nebulisers in a representative number of patients; hence, there was no formal statistical basis for the size of the patient population, and descriptive statistics were initially planned to summarise the data. Subsequently, a *post-hoc* random-effect analysis of variance to assess the devices' effects on nebulisation time and PK parameters was performed. The coefficient of determination (r^2) was used to assess relationships between the deposition of tobramycin in the lungs and tobramycin PK parameters in serum. r^2 gives the proportion of the variance in serum PK parameters explained by drug deposition in the lung. All clinical data management, transformation, and analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient demographics and baseline characteristics

Thirteen subjects (six healthy volunteers and seven CF patients) were enrolled. One CF patient withdrew consent and did not complete the study. The deposition- and pharmacokinetics-evaluable populations consisted of all six healthy volunteers and the six CF patients who completed the study. The mean BMI for healthy subjects was 26 and that for the CF patients was 20.5. The FEV_1 prior to any dose administration for each treatment group is shown in Table 1. None of the healthy volunteers had a history of respiratory disorder or previous treatment with tobramycin or other inhaled aminoglycosides, whereas 29% (n=2) of the CF patients had previously used tobramycin (Table 1).

3.2. Aerosol delivery

Whole-lung deposition of tobramycin (in terms of median percentage of metered dose) was similar with the eFlow *rapid* and LC Plus in healthy volunteers (13.3±6.5% and 14.8±1.8%, Table 2). In CF patients, whole-lung deposition was approximately 40% less with the eFlow *rapid* compared to the LC Plus

Table 1
Demographic summary by treatment group (ITT population).

	Healthy volunteers (N=6)		CF patients (N=7)	
	eFlow/ LC	LC/ eFlow	eFlow/ LC	LC/ eFlow
Age (in years)	33.3 (9.5)	44.3 (11.2)	21.8 (4.3)	21.3 (3.1)
Male, n (%)[a]	3 (100)	3 (100)	2 (50)	2 (67)
Female, n (%)[a]	0	0	2 (50)	1 (33)
Mean BMI	24.6	27.2	20.4	20.5
Inhaled tobramycin prior to study	0	0	0	2
Inhaled other aminoglycosides prior to study	0	0	1	1
Mean pre-dose FEV_1% predicted at period 1	99.2	93.2	65.5	53.3

Values for age, weight, and height are mean (standard deviation).
BMI, body mass index.
[a] Since this was a crossover study, a patient randomised to inhale tobramycin with eFlow *rapid* in the first period will also receive tobramycin with LC Plus in the second period, and vice versa. Therefore a total of 6 male healthy volunteers and 7 CF patients received tobramycin with both LC Plus and eFlow *rapid*.

Table 2
Distribution of tobramycin activity in the whole-lung, oropharynx, devices, and exhaled air (deposition-evaluable patients).

	LC Plus		eFlow *rapid*	
	Healthy (N=6)	CF (N=6)	Healthy (N=6)	CF (N=6)
Median% metered dose (SD)				
Whole-lung	14.8 (1.8)	15.1 (6.0)	13.3 (6.5)	8.9 (0.8)
Oropharynx [a]	8.5 (1.8)	7.5 (5.8)	4.4 (3.5)	5.1 (3.4)
Device	58.6 (13.5)	57.5 (25.5)	52.2 (10.1)	65.2 (11.1)
Exhaled air [b]	20.5 (12.2)	20.5 (15.8)	25.0 (11.3)	24.5 (8.7)
Drug deposited (mg)				
Whole-lung	44.3 (5.5)	45.2 (18.1)	40.0 (19.5)	26.6 (2.5)
Oropharynx [a]	25.4 (5.5)	22.4 (17.5)	13.1 (10.5)	15.2 (10.1)
Device	175.8 (40.4)	172.5 (76.5)	156.5 (30.2)	195.6 (33.3)
Exhaled air [b]	61.4 (36.5)	70.1 (43.3)	74.8 (33.8)	73.5 (26.0)

Drug deposition values are expressed as median (standard deviation).
CF, cystic fibrosis.
[a] Sum of esophagus, oropharynx and stomach.
[b] Sum of exhalation filter, mouthpiece, T-piece, scavenger filter, and tissues.

device (8.9±0.8%, and 15.1±6.0%, respectively). This difference was not statistically significant ($p>0.05$, $n=6$). The amount of tobramycin remaining in either device was similar in healthy subjects. Oropharyngeal deposition was low for both nebulisers (<10% of the total) and in both populations (Table 2).

Tobramycin distribution across the different zones of lung was similar between the nebulisers for both CF patients and healthy volunteers (Table 3). The highest deposition within the lungs occurred in the most central lung region (lung region 1) for both the devices and for both groups of subjects. An illustration of the various zones can be found in Fig. 1. In order to quantify the regional lung deposition, the Airway Penetration Factor (APF) was estimated. APF is defined as the activity concentration (radioactivity counts per unit area) for a region divided by the average activity concentration for all six regions [15]. The mean APF were reasonably similar in regions 1–4 (greater than 1.0, with region 1 being the most central) for both groups of subjects and with both devices. This suggests that the central zone as depicted in Fig. 1 has greater than average activity concentration. In contrast, in the most peripheral lung regions, that is regions 5 and 6, the mean APFs were <1.0 (Table 3).

Table 3
Distribution of tobramycin activity between the different zones of the lungs (deposition-evaluable population).

Lung Zones	LC Plus		eFlow *rapid*	
	Healthy (N=6)	CF (N=6)	Healthy (N=6)	CF (N=6)
% Metered dose				
1	3.8 (0.5)	3.9 (1.3)	2.9 (1.5)	2.6 (0.5)
2	1.6 (0.2)	1.6 (0.6)	1.2 (0.7)	1.0 (0.1)
3	2.1 (0.3)	2.1 (0.7)	1.8 (0.8)	1.3 (0.2)
4	2.7 (0.4)	2.8 (1.0)	2.3 (1.2)	1.6 (0.3)
5	2.7 (0.4)	3.0 (1.5)	2.8 (1.2)	1.6 (0.4)
6	1.5 (0.5)	1.8 (1.1)	2.3 (1.1)	1.1(0.3)
Drug deposited (mg)				
1	11.3 (1.6)	11.6 (4.0)	8.8 (4.5)	7.7 (1.4)
2	4.9 (0.7)	4.7 (1.7)	3.7 (2.1)	2.9 (0.3)
3	6.3 (0.9)	6.3 (2.1)	5.4 (2.5)	3.9 (0.5)
4	8.0 (1.1)	8.4 (3.1)	7.0 (3.5)	4.7 (1.0)
5	7.9 (1.3)	8.9 (4.4)	8.1 (3.6)	4.7 (1.1)
6	4.5 (1.4)	5.4 (3.3)	6.9 (3.4)	3.3 (0.9)
Airway penetration factors				
1	1.3 (0.1)	1.2 (0.1)	1.2 (0.1)	1.4 (0.4)
2	1.3 (0.1)	1.2 (0.04)	1.2 (0.1)	1.3 (0.03)
3	1.2 (0.1)	1.2 (0.1)	1.2 (0.03)	1.2 (0.1)
4	1.1 (0.1)	1.1 (0.02)	1.1 (0.1)	1.1 (0.1)
5	0.8 (0.1)	0.8 (0.1)	0.9 (0.03)	0.7 (0.1)
6	0.3 (0.1)	0.4 (0.1)	0.5 (0.1)	0.3 (0.1)

Values are expressed as median (standard deviation).
CF, cystic fibrosis.

For the healthy volunteers, dosing was interrupted in three subjects with eFlow *rapid* but not with LC Plus. Dosing was interrupted in 43% ($n=3$) of CF patients when using eFlow *rapid* and in 33% ($n=2$) when using the LC Plus device. Interruptions among CF patients were mainly due to coughing. All subjects were able to complete the nebulisation procedure. The nebulisation and dosing times (which included the time when dose was interrupted) were reduced with eFlow *rapid* in all subjects. The median nebulisation times for eFlow *rapid* compared with LC Plus were 7.5 versus 16.0 min ($p<0.01$) in healthy volunteers and 7.0 versus 20.0 min ($p<0.05$) in CF patients. The median dosing times for eFlow *rapid* versus LC Plus nebuliser were 8.5 versus 16.0 min for healthy volunteers and 8.0 versus 20.0 min for CF subjects. Relative difference between recorded nebulisation time and dosing time was greater with eFlow *rapid* than with LC Plus in both groups due to dosing interruptions (12–13% with eFlow *rapid*, 0–1% with LC Plus).

3.3. Pharmacokinetics

The pre-defined drug concentration thresholds that may be associated with systemic toxicity were not exceeded by any subject or patient using either of the nebulisers. The mean tobramycin C_{max} ranged from 0.6 to 1.2 μg/mL and occurred between 0.5 and 2 h after nebulisation (Table 4). In healthy subjects, tobramycin AUC_{0-8} was similar with both nebulisers (3.3±0.7 and 3.6±1.9 μg h/mL for LC Plus and eFlow *rapid*, respectively [$p=0.96$]), whereas in CF patients, it was lower for eFlow *rapid* (1.9±0.8 μg h/mL) as compared with LC Plus (5.0±3.0 μg h/mL; $p<0.01$). C_{max} was also lower for eFlow *rapid*

Table 4
Tobramycin pharmacokinetics (pharmacokinetics-evaluable population).

Parameter	Healthy subjects		CF patients	
	LC Plus	eFlow *rapid*	LC Plus	eFlow *rapid*
t_{max} (h)	1 (1–2)	1 (1–2)	1 (0.5–2)	1 (0.5–1)
C_{max} (μg/mL)	0.6±0.2	0.7±0.4	1.2±0.6	0.5±0.2
AUC_{0-8} (μg h/mL)	3.3±0.7	3.6±1.9	5.0±3.0	1.9±0.8
$t_{1/2}$ (h)	5.8±2.0	4.6±1.2	2.7±1.1	2.7±0.7

Values are arithmetic mean±standard deviation except for t_{max} which is median (range).
t_{max}, time to reach maximum concentration; C_{max}, peak serum drug concentration; AUC_{0-8}, area under the curve from time 0 to 8 h; $t_{1/2}$, half-life and CF, cystic fibrosis.

as compared with LC Plus in CF patients ($p<0.05$). The $t_{1/2}$ values were independent of the type of nebuliser used in CF patients and healthy volunteers, although $t_{1/2}$ values were longer in the healthy subjects. Based on r^2, the percentage drug deposition in the lungs was predictive of the systemic peak drug exposure using eFlow *rapid* ($r^2=0.85$) but not for LC Plus ($r^2=0.19$) in healthy volunteers. In CF patients, lung deposition was highly predictive of peak drug exposure for LC Plus ($r^2=0.92$) but not for eFlow *rapid* ($r^2=0.39$). In both groups, the stronger correlation was observed for the nebuliser that yielded the wider range of C_{max} values. Hence, the weaker correlations may have resulted from too narrow an exposure range to robustly assess the association between deposition of drug in the lung with systemic drug exposure.

3.4. Safety

AEs were observed in both healthy volunteers and CF patients with both nebulisers. Most of the AEs were mild and transient and gave no indication of target organ toxicity. Respiratory disorders were the most commonly reported AEs. The frequency of AEs was higher among CF patients ($n=3$) than healthy volunteers ($n=1$) while using LC Plus. One CF patient during the treatment period with LC Plus was hospitalised due to fluctuation in blood glucose and weight loss. With eFlow *rapid* nebuliser, the incidence rates of AEs were similar in both treatment groups. One healthy volunteer experienced skin rash with eFlow *rapid*, which was suspected to be study drug related. The most common respiratory tract AE reported by CF patients was cough (eFlow *rapid* [$n=3$] and LC Plus [$n=1$]). In CF group, one patient experienced a >10% reduction in FEV_1 after using both inhalers. No patient experienced clinically significant bronchospasm (decrease in FEV_1 of >20%).

4. Discussion

The clinical effect of aerosolised drugs depends on the dose reaching the site of action. The administration of aerosolised antibiotics is most often given using breath-enhanced nebuliser systems such as LC Plus [12]. The LC Plus nebuliser is the approved device for administering tobramycin in CF patients with chronic endobronchial infections caused by *P. aeruginosa* [18]. Ramsey et al. [19] reported that in combination with an appropriate compressor it increased the aerosol delivery of tobramycin, a finding corroborated by others [20,21]. The LC Plus is superior to many other jet nebulisers with respect to the time required for nebulisation [22], but the delivery of tobramycin (300 mg) takes more than 15 min, imposing a significant burden on CF patients [9]. Improvements in aerosol delivery systems have allowed shorter nebulisation times, which may improve patient compliance and quality of life [23]. Although this study was conducted in a small patient population, it provides initial evidence that the PARI eFlow *rapid* nebuliser has a shorter nebulisation time.

In the present study, whole-lung deposition of tobramycin in this study was similar with both devices in healthy volunteers, but was approximately 40% lower in CF patients using the eFlow *rapid*. More tobramycin also remained in the eFlow *rapid* device after it was used by the CF patients. This could be the result of shallow breathing that may occur in CF patients, leaving more time for small droplets to coalesce and be deposited on the device surface. Another factor is that, unlike the LC Plus, there is no compressor attached to the eFlow *rapid* device. The variability seen between the eFlow *rapid* and the LC Plus in CF patients may be attributed to the difference in handling of the nebulisers between healthy subjects and CF patients, especially with a system that delivers the drug over a shorter nebulisation time. Patients should therefore be coached to handle the nebulisers correctly, inhale deeply and slowly [24]. The wide variability in lung deposition patterns with eFlow *rapid* did not allow firm conclusions to be drawn with respect to this device. In addition, the distribution of different degrees of lung function in CF patients and its influence on drug deposition patterns need to be evaluated in larger patient populations for better understanding of this aspect.

In vitro laboratory data using simulated breathing patterns to deliver tobramycin [25,26] showed that the eFlow *rapid* produced a mass median aerodynamic diameter (MMAD) about 10% higher than the LC Plus (mean±SD=3.95±0.07 μm versus 3.54±0.06 μm) and a narrower particle size distribution pattern than the LC Plus nebuliser (geometric standard deviation [GSD]±SD=1.47±0.02 μm versus 2.10±0.01 μm). The influence of 99mTc DTPa on the particle size distribution of tobramycin aerosol has not been estimated in this study. This is an acknowledged limitation of the present study. The amount of 99mTc added to tobramycin was not more than 20 MBq 99mTc DTPA. Coates et al. [27] have shown that the radiolabel and the drug track together and the values for MMAD and GSD obtained in this paper are similar to the values reported in this study. In addition to this study, it has been assumed that Tc nebulisation parallels tobramycin nebulisation. During nebulisation, it is possible that the concentration of the nebulised solution may increase due to preferential nebulisation of the smaller molecules. The tobramycin concentration in the remaining solution in the nebuliser could be usually higher by the end of nebulisation. The previous factors could have an influence on the study results and need further investigation.

The small patient population and large interpatient variability in the scintigraphic measurements preclude conclusions on potential differences in lung deposition between the two devices. For both devices, tobramycin was deposited across all regions with higher than average deposition in the central areas than in the peripheral regions. This observational study was conducted in a small number of CF patients with screening %predicted $FEV_1 \geq 25\%$. No power calculations were performed to assess the impact of lung function of drug deposition in lungs. Further studies on larger patient populations will help to assess this parameter in CF patients.

The pre-specified threshold serum concentrations, which might predispose patients to systemic toxicity, were not exceeded in any subject using either nebuliser. C_{max} of tobramycin and AUC_{0-8} were in the range of exposures seen in previous PK studies with these two nebulisers [28]. In healthy subjects,

systemic tobramycin exposure was comparable between the two nebulisers. In CF patients, it was lower with the eFlow *rapid*, possibly reflecting the relatively lower whole-lung deposition. Currently, there is no consensus on toxic serum tobramycin levels when the drug is administered by inhalation. In our protocol, we used the criteria often applied to intravenous tobramycin administration given three times daily [29], although whether these criteria are appropriate to tobramycin by inhalation is not currently known. Irrespective of this, the highest serum tobramycin concentration measured in the current study in any subject or patient at any time point was 1.9 μg/mL.

We have shown in this exploratory study that the eFlow *rapid* nebuliser reduced the dosing times although with less tobramycin deposited in the whole-lung in CF patients compared with the LC Plus device. It is probable that deposition is less with eFlow *rapid* in CF patients. However, this study was under powered due to its smaller patient population. Hence, additional studies with larger number of patients are needed to evaluate the performance and clinical benefit, in terms of efficacy, of eFlow *rapid* compared to the currently approved LC plus device.

Conflict of interest statement

WL and FE have no conflicts of interest with respect to this study. JMK and PK are employees of Novartis.

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